Amendment to the Claims:

Please amend the claims as follows.

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

Claim 1 (previously presented): A method for producing a recombinant antibody or antigen binding fragment with improved yield from a host cell, comprising:

(i) providing a nucleic acid encoding a modified non-human antibody or antigen binding fragment made by a method comprising:

(a) aligning a hypervariable region (HVR1) and/or a hypervariable region 2 (HVR2) of a variable domain of a non-human antibody or antigen binding fragment to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences;

(b) selecting a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the non-human HVR1 sequence and/or the non-human HVR2 sequence;

(c) identifying at least one amino acid position in at least one framework region (FR) of the selected human subgroup variable domain consensus sequence that has a different amino acid residue than that of a corresponding position in a FR of the variable domain of the non-human antibody or antigen binding fragment; and

(d) modifying one amino acid at the corresponding position of the non-human variable domain of the antibody or antigen binding fragment to be the same as the different human amino acid residue identified in (c) to form a modified FR region in the non-human variable domain of the antibody or antigen binding fragment; and

(ii) expressing the modified non-human antibody or antigen binding fragment in the host cell,

wherein the modified non-human antibody or antigen binding fragment has improved yield in a cell or a cell culture as compared to the corresponding unmodified antibody or antigen binding fragment.

Claim 2 (previously presented): The method according to claim 1, wherein the non-human antibody or antigen binding fragment to be modified is selected from the group consisting of a humanized antibody, a chimeric antibody, a monoclonal antibody, a multispecific antibody, a diabody, or an antibody generated by phage display.

Claim 3 (previously presented): The method according to claim 2, wherein the non-human antigen binding fragment is a Fab fragment, $F(ab')_2$ fragment, scFV fragment, or $sc(Fv)_2$ fragment, a single arm antibody or single chain antibody.

Claim 4 (previously presented): The method according to claim 1, wherein the non-human antibody is an anti-VEGF antibody.

Claim 5 (previously presented): The method according to claim 4, wherein the non-human antibody is a humanized antibody.

Claim 6 (canceled)

Claim 7 (previously presented): The method of claim 1, wherein the nucleic acid encoding the modified non-human antibody or antigen binding fragment further comprises a nucleic acid encoding a constant region domain, and the constant region domain-encoding nucleic acid is connected to the antibody or antigen binding fragment-encoding nucleic acid to form a nucleic acid encoding a full-length heavy and/or light chain.

Claim 8 (previously presented): The method of claim 1, wherein the host cell comprises an expression vector comprising the nucleic acid encoding the modified non-human antibody or antigen binding fragment.

Claim 9 (previously presented): The method of claim 7, further comprising recovering a modified non-human full-length heavy or light chain or both from the culture.

Claim 10 (previously presented): The method according to claim 1, wherein the host cell is a prokaryotic host cell.

Claim 11 (previously presented): The method according to claim 1, wherein the host cell is a mammalian cell.

Claim 12 (previously presented): The method according to claim 1, further comprising isolating the expressed non-human heavy chain variable domain having a modified FR region or the modified non-human light chain variable domain having a modified FR region.

Claim 13 (previously presented): The method according to claim 12, wherein the non-human variable domain is a heavy chain variable domain and the HVR1 amino acid sequence of the heavy chain variable domain of the antibody or antigen binding fragment is GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO:18).

Claim 14 (previously presented): The method according to claim 1, wherein the non-human framework region to be modified is selected from the group consisting of a FR1, a FR2, a FR3, a FR4 and a mixture thereof.

Claim 15 (previously presented): The method according to claim 14, wherein the human subgroup variable domain consensus sequence comprises a variable domain FR1 sequence with a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:3.

Claim 16 (previously presented): The method according to claim 1, wherein the yield of the non-human antibody or antigen binding fragment comprising the modified FR is improved at least 2 fold compared to the corresponding unmodified antibody or antigen binding fragment.

Claim 17 (previously presented): The method according to claim 16, wherein the yield of the non-human antibody or antigen binding fragment comprising the modified FR is improved at least 2 fold to 16 fold compared to the corresponding unmodified antibody or antigen binding fragment.

Claim 18 (previously presented): The method of claim 1, wherein two, three, four, five, six or seven amino acid positions in the non-human FR are modified.

Claim 19 (previously presented): The method of claim 1, wherein the non-human antibody or antigen binding fragment is a VEGF antibody or antigen binding fragment comprising a heavy chain variable domain FR1 sequence of SEQ ID NO:3, and the FR is a heavy chain variable domain FR1 and one of the amino acid positions is position 6 or position 23 or both, and the other position is selected from the group consisting of position 1, 11, 13, 18, 19, and a mixture thereof.

Claim 20 (previously presented): The method of claim 19, wherein amino acid positions 6 and 23 are modified.

Claim 21 (previously presented): The method of claim 19, wherein the amino acid positions at positions 1, 6, 11, 13, 18, 19, and 23 of the heavy chain FR1 are modified.

Claim 22 (previously presented): The method of claim 1, wherein at least one but not all of the amino acid positions in the non-human FR are modified.

Claim 23 (previously presented): The method of claim 22, wherein the modified FR is FR1, FR2, or FR3.

Claim 24 (previously presented): The method of claim 1, wherein at least one but not all of the amino acid positions that have a different amino acid as compared to the human consensus sequence in all framework regions (FRs) of the non-human variable region are modified.

Claim 25 (currently amended): A method for preparing a humanized antibody or an antigen binding fragment having an improved folding efficiency and yield when expressed in a host cell, comprising:

(a) preparing a humanized antibody or antigen binding fragment comprising a variable domain comprising at least one modified framework (FR) sequence, wherein the variable domain is made by a method comprising:

(i) aligning a hypervariable region (HVR1) and/or a hypervariable region 2 (HVR2) of a variable domain of a non-human antibody or antigen binding fragment to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences;

(ii) selecting a human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the non-human HVR1 sequence and/or the non-human HVR2 sequence;

(iii) identifying at least one amino acid position in at least one framework region (FR) of the ~~selected~~ human subgroup variable domain consensus sequence selected in step (ii) that has a different amino acid residue than that of a corresponding position in a FR of the variable domain or antigen binding fragment of the non-human antibody; and

(iv) modifying one amino acid at the corresponding position of the non-human variable domain or antigen binding fragment of the antibody to be the same as the different human amino acid residue identified in (c) to form a modified FR region in the non-human variable domain or antigen binding fragment of the antibody,

wherein the modification results in an antibody or antigen binding fragment having an improved folding efficiency and yield when expressed in the host cell, and

(b) expressing the modified humanized antibody or modified antigen binding fragment in the [[a]] host cell.

Claims 26 to 27 (canceled)

Claim 28 (previously presented): The method according to claim 25 wherein the non-human variable domain is a heavy chain variable domain and the HVR1 amino acid sequence of a heavy chain variable domain of the non-human antibody or antigen binding fragment is GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO:18).

Claim 29 (previously presented): The method according to claim 25, wherein the FR is selected from the group consisting of a FR1, a FR2, a FR3, a FR4 and a mixture thereof.

Claim 30 (previously presented): The method according to claim 29, wherein the human subgroup variable domain consensus sequence comprises a heavy chain variable domain FR1 sequence with a sequence selected from the group consisting of SEQ. ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3.

Claim 31 (previously presented): The method of claim 25, wherein at least one but not all of the amino acid positions in the non-human FR are modified.

Claim 32 (previously presented): The method of claim 25, wherein the humanized antibody or antigen binding fragment has improved yield when produced in the cell or cell culture as compared to a non-human antibody or antigen binding fragment having the same HVR1 and/or HVR2 but without the modified FR.

Claim 33 (previously presented): The method of claim 25, wherein the host cell comprises an expression vector comprising the nucleic acid encoding the modified non-human antibody or antigen binding fragment.

Claim 34 (previously presented): The method of claim 33, wherein the nucleic acid further comprises a sequence encoding a constant domain connected to the nucleic acid encoding the modified non-human antibody or antigen binding fragment to form a nucleic acid encoding a full-length heavy or light chain.

Claim 35 (canceled)

Claim 36 (previously presented): The method according claim 25, wherein the host cell is a prokaryotic host cell.

Claim 37 (previously presented): The method according to claim 25, wherein the host cell is a mammalian cell.

Claim 38 (currently amended): A method for improving the yield of an assembled non-human monoclonal antibody or antigen binding fragment in a host cell, comprising:

(a) aligning a hypervariable region 1 (HVR1) and/or a hypervariable 2 (HVR2) sequence of a heavy chain variable domain of the non-human monoclonal antibody to corresponding HVR1 and/or HVR2 sequences of human subgroup heavy chain variable domain consensus sequences,

(b) selecting a human subgroup heavy chain variable domain consensus sequence that has the HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or the HVR2 sequence of the heavy chain variable domain of the non human monoclonal antibody,

(c) modifying at least one but not all amino acid positions in at least one framework (FR) of the non-human monoclonal antibody heavy chain variable domain to an amino acid residue found at a corresponding position of the selected human subgroup heavy chain variable domain consensus sequence to form at least one modified FR, wherein the non-human monoclonal antibody or antigen binding fragment with the modified FR has improved folding efficiency and yield, in cell culture compared to the folding efficiency and yield of a corresponding unmodified antibody or antigen binding fragment; and

(d) expressing the non-human monoclonal antibody or antigen binding fragment comprising the modified FR in the host cell.

Claim 39 (currently amended): A method for improving the yield of a recombinant antibody or antigen binding fragment expressed in a host cell, comprising:

(a) selecting a human subgroup variable domain consensus sequence by aligning a hypervariable region 1 (HVR1) and/or a hypervariable 2 (HVR2) sequence of a variable domain of a non-human antibody or antigen binding fragment thereof to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences, and selecting the human subgroup variable domain consensus sequence that has the HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or HVR2 sequence of the variable domain of the non-human antibody or antigen binding fragment thereof, and

(b) modifying at least one but not all amino acid residues in the framework (FR) of the variable domain of the non-human antibody or antigen binding fragment such that the modified FR has at least 50% sequence identity to the corresponding FR amino acid sequence of the selected human subgroup variable domain consensus sequence to form a modified FR,

wherein the amino acid residues in the framework (FR) are modified to the amino acid residue of the corresponding human subgroup variable domain consensus sequence amino acid,

and the antibody or antigen binding fragment with the modified FR has improved folding efficiency and yield, in cell culture compared to the folding efficiency and yield of a corresponding unmodified antibody or antigen binding fragment;

(c) expressing the antibody or antigen binding fragment with the modified FR in the host cell and recovering the antibody or antigen binding fragment with the modified FR from the host cell.

Claim 40 (previously presented): The method according to claim 39, wherein the variable domain is a heavy chain variable domain and the HVR1 amino acid sequence of a heavy chain variable domain of the antibody or antigen binding fragment is GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO: 18).

Claim 41 (previously presented): The method of claim 39, wherein at least two but not all amino acid positions that have a different amino acid in at least one FR are substituted with amino acids in the corresponding position of the selected human subgroup consensus sequence.

Claim 42 (previously presented): The method of claim 41, wherein the antibody or antibody binding fragment is a VEGF antibody or antibody binding fragment comprising a heavy chain variable domain FR1 comprising the amino acid sequence of SEQ ID NO:3 and amino acid positions 6 and 23 of heavy chain FR1 are modified.

Claim 43 (previously presented): The method of claim 42, wherein amino acid positions 1, 6, 11, 13, 18, 19 and 23 of the heavy chain FR1 are modified.

Claim 44 (previously presented): The method of claim 38, wherein the host cell comprises an expression vector comprising the nucleic acid encoding the modified non-human antibody or antigen binding fragment modified FR.

Claim 45 (previously presented): The method according to claim 44, wherein

(i) the expression vector further comprises a second nucleic acid encoding a constant domain,

(ii) the method of (i), wherein the first nucleic acid and the second nucleic acid are operably linked to a promoter;

(iii), the method of (i) or (ii), wherein the first and/or second nucleic acid are operably linked to a heat stable enterotoxin sequence that can direct secretion to the periplasm; or

(iv), the method of any of (i) to (iii), wherein the first or second nucleic acid are operably linked to a terminator sequence.

Claim 46 (previously presented): The method according to claim 38, wherein the host cell is a prokaryotic host cell.

Claim 47 (previously presented): The method according to claim 38, wherein the host cell is a mammalian cell.

Claim 48 (previously presented): The method according to claim 39, wherein the step of modifying comprises modifying one but not all amino acid residues in all of the FRs of the variable domain with amino acid residues of the corresponding human subgroup variable domain consensus sequence.

Claim 49 (previously presented): The method according to claim 38, wherein the framework region sequence is selected from the group consisting of FR1, FR2, FR3, FR4 and a mixture thereof.

Claim 50 (currently amended): A method for producing an antibody or an antigen binding fragment expressed with improved yield from a host cell comprising:

(a) aligning a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) sequence of a non-human monoclonal antibody to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences,

(b) selecting a human subgroup variable domain consensus sequence that has the HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or HVR2 sequence of the non human monoclonal antibody,

(c) identifying at least one amino acid position proximal to a cysteine (cys) residue that participates in an intrachain variable domain disulfide bond in the selected human subgroup variable domain consensus sequence having a different amino acid than that found at a corresponding position of the non-human antibody or antigen binding fragment's variable domain,

(d) modifying the amino acid at the corresponding position of the non-human antibody or antigen binding fragment with the different amino acid of the selected human subgroup variable domain consensus sequence to form a modified variable domain; and

(e) expressing the antibody or antigen binding fragment comprising the modified variable domain in the host cell,

wherein the modified antibody or antigen binding fragment has improved folding efficiency and yield, in cell culture as compared to the folding efficiency and yield of an unmodified antibody or antigen binding fragment.

Claim 51 (original): The method according to claim 50, wherein the variable domain is a heavy chain variable domain or a light chain variable domain.

Claim 52 (previously presented): The method according to claim 51, wherein the antibody or antigen binding fragment has the framework regions from the human light chain variable domain Kappa subgroup I consensus sequence comprising the amino acid sequence of amino acids 1 -23, 35-49, 57-88, and 98-107 of SEQ ID NO:25 , and the position modified is the amino acid position 4 of the light chain, the amino acid position 6 of the light chain, the amino acid position 33 of the light chain, the amino acid position 35 of the light chain, or the amino acid position 71 of the light chain.

Claim 53 (previously presented): The method according to claim 51, wherein the antibody or antigen binding fragment is modified with amino acid residues corresponding to framework regions from the human heavy chain variable domain subgroup III consensus sequence comprising the amino acid sequence of amino acids 215-240, 251-264, 271-309, and 318-328 of SEQ ID NO:25, and the position modified corresponds to amino acid position 4 of the heavy chain, the amino acid position 6 of the heavy chain, the amino acid position 34 of the heavy chain, the amino acid position 36 of the heavy chain, the amino acid position 78 of the heavy chain, or the amino acid position 104 of the heavy chain.

Claim 54 (previously presented): The method according to claim 51, wherein the antibody or antigen binding fragment is modified with amino acid residues corresponding to framework regions from the human light chain variable domain Kappa subgroup I consensus sequence comprising the amino acid sequence of amino acids 1 -23, 35-49, 57-88, and 98-107 of SEQ ID NO:25, and is modified with amino acid residues corresponding to framework regions from the human heavy chain variable domain subgroup III consensus sequence comprising the amino acid sequence of amino acids 215-240, 251-264, 271-309, and 318-328 of SEQ ID NO:25, and the at least one position is selected from the group consisting of amino acid position 4 of the light chain, amino acid position 6 of the light chain, amino acid position 33 of the light chain, amino acid position 35 of the

light chain, amino acid position 71 of the light chain, and at least one position corresponds to amino acid position 4 of the heavy chain, amino acid position 6 of the heavy chain, amino acid position 34 of the heavy chain, amino acid position 36 of the heavy chain, amino acid position 78 of the heavy chain, and amino acid position 104 of the heavy chain.

Claim 55 (previously presented): The method according to claim 50, wherein the one amino acid position is an amino acid position adjacent to the cysteine (cys) residue that forms an intra chain variable domain disulfide bond.

Claim 56 (previously presented): The method according to claim 55, wherein the one amino acid position corresponds to amino acid position 21, amino acid position 22, amino acid position 24, amino acid position 25, amino acid position 86, amino acid position 87, amino acid position 89 or amino acid position 90 in a light chain variable domain of SEQ ID NO: 25.

Claim 57 (previously presented): The method according to claim 55, wherein the one amino acid position corresponds to amino acid position 20, amino acid position 21, amino acid position 23, amino acid position 24, amino acid position 90, amino acid position 91, amino acid position 93 or amino acid position 94 in a heavy chain variable domain of SEQ ID NO: 25.

Claim 58 (previously presented): The method according to claim 50, wherein the non-human variable domain is from an anti-VEGF antibody.

Claim 59 (previously presented): The method according to claim 50, wherein the non-human variable domain is from a humanized antibody or antigen binding fragment.

Claim 60 (previously presented): The method according to claim 50, wherein the host cell comprises an expression vector comprising a nucleic acid encoding the modified variable domain.

Claim 61 (previously presented): The method according to claim 60, wherein: (a) the expression vector further comprises a second nucleic acid encoding an antibody constant region domain, (b) the nucleic acid encoding the modified variable domain and the second nucleic acid are operably linked to a promoter; (c) the method of (a) or (b), wherein the nucleic acid further comprises a heat stable enterotoxin sequence that can direct secretion to a host cell periplasm; or (d) the method of any of (a) to (c), wherein the nucleic acid further comprises a terminator sequence.

Claim 62 (canceled)

Claim 63 (previously presented): The method according to claim 60, wherein the heavy chain variable domain is from an anti-VEGF antibody and comprises the amino acid sequence of amino acids 215 -328 of SEQ ID NO:5 or SEQ ID NO:7, and has a substitution in an amino acid position corresponding to an amino acid position selected from the group consisting of 4, 6, 34, 78, and a mixture thereof.

Claim 64 (previously presented): The method of claim 60, wherein the light chain variable domain is from an anti-VEGF antibody and comprises the amino acid sequence of amino acids 1-107 of SEQ ID NO:5 or SEQ ID NO:7, and has a substitution in amino acid position 4, 71, or a mixture thereof.

Claim 65 (previously presented): The method according to claim 50, wherein the host cell is a prokaryotic host cell.

Claim 66 (previously presented): The method according to claim 50, wherein the host cell is a eukaryotic host cell.

Claim 67 (previously presented): The method according to claim 50, wherein the expressed antibody or antigen binding fragment with modified variable domain has increased yield of at least

2 fold when produced in cell culture as compared to the unmodified antibody or antigen binding fragment.

Claim 68 (previously presented): The method according to claim 67, wherein the yield of the expressed antibody or antigen binding fragment with the modified variable domain is increased at least 2 to 16 fold as compared to the unmodified antibody or antigen binding fragment.

Claim 69 (previously presented): The method of claim 50 further comprises:

(a) identifying at least one amino acid position in a second variable domain of the non-human antibody or antigen binding fragment that is proximal to a cysteine (cys) residue that participates in an intrachain variable domain disulfide bond in the second variable domain;

(b) selecting a human subgroup variable domain consensus sequence having the most sequence identity with a HVR1 and/or HVR2 amino acid sequence of the second non-human variable domain; and

(c) determining whether the amino acid in the amino acid position identified in the second non-human variable domain is different than the amino acid in the selected human subgroup variable domain consensus sequence; and

(d) placing at the at least one position in the second non-human variable domain the different amino acid found at the corresponding position in the selected human subgroup variable domain consensus sequence to form a modified variable domain.

Claim 70 (previously presented): The method of claim 69, wherein the non-human variable domain is a heavy chain variable domain and the second non-human variable domain is a light chain variable domain.

Claim 71 (previously presented): A method for preparing a humanized non-human monoclonal antibody or antigen binding fragment, comprising:

(a) modifying at least one amino acid position proximal to a cysteine (cys) residue that participates in an intrachain variable domain disulfide bond in a non-human variable domain with a

different amino acid, wherein the different amino acid is determined by aligning the a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) sequence of a non-human monoclonal antibody to corresponding HVR1 and/or HVR2 sequences of human subgroup consensus sequences, and selecting the amino acid found at the corresponding position of the human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or HVR2 amino acid sequence of the non-human monoclonal antibody as the different amino acid to form a modified variable domain;

(b) expressing a humanized antibody or antigen binding fragment comprising the modified variable domain in a host cell; and

(c) recovering the modified humanized antibody or antigen binding fragment from the host cell.

Claim 72 (previously presented): The method according to claim 71, wherein the non-human variable domain is a heavy chain variable domain.

Claim 73 (previously presented): The method according to claim 71, wherein the non-human variable domain is a light chain variable domain.

Claim 74 (currently amended): A method for improving the yield of an antibody or fragment thereof, comprising:

(a) identifying at least one amino acid position in a non-human heavy chain variable domain that is proximal to a cysteine (cys) residue that participates in an intrachain disulfide bond in the heavy chain variable domain;

(b) aligning a hypervariable 1 (HVR1) and/or hypervariable region 2 (HVR2) of the non-human heavy chain variable domain of step a) to corresponding HVR1and/or HVR2 sequences of human subgroup heavy chain variable domain consensus sequences;

(c) selecting a human subgroup heavy chain variable domain consensus sequence having the most identity with the HVR1 and/or HVR2 amino acid sequence of the non-human heavy chain variable domain; and

(d) modifying the selected position in the non-human heavy chain variable domain an amino acid with the corresponding position in the selected human subgroup heavy chain variable domain consensus sequence to form a modified non-human heavy chain variable domain;

(e) identifying at least one amino acid position in a non-human light chain variable domain that is proximal to a cysteine (cys) residue that participates in an intrachain disulfide bond in the light chain variable domain;

(f) aligning a HVR1 and/or HVR2 of the light chain variable domain of step e) to corresponding HVR1 and/or HVR2 sequences of human subgroup light chain variable domain consensus sequences;

(g) selecting a human subgroup light chain variable domain consensus sequence having the most sequence identity with the HVR1 and/or HVR2 amino acid sequence of the non-human light chain variable domain;

(h) modifying the selected position in the non-human light chain variable domain an amino acid with the corresponding position in the selected human subgroup light chain variable domain consensus sequence to form a modified non-human light chain variable domain; and

(i) expressing the antibody or antibody fragment thereof comprising the modified non-human heavy chain variable domain and the modified non-human light chain variable domain in a host cell, wherein the modified antibody or antibody fragment thereof has improved folding efficiency and yield in the host cell as compared to the folding efficiency and yield of an unmodified antibody or antibody fragment.

Claims 75 to 95 (canceled)

Claim 96 (currently amended): A method for improving the yield of antibody or antigen binding fragment in a host cell or cell culture, comprising:

a) expressing a nucleic acid encoding a variable domain of a non-human antibody or antigen binding fragment comprising at least one modified framework (FR) in the host cell, wherein the modified FR has: (i) a substitution of at least one but not all amino acids in the at least one FR with a different amino acid, or (ii) a deletion of at least one but not all amino acids in the FR,

wherein the amino acid residue or residues to be substituted or deleted is determined by aligning a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) sequence of the non-human variable domain of the antibody or antigen binding fragment to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences, and selecting the amino acid found at the corresponding FR position of the human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or HVR2 sequence of the non-human variable domain of the antibody or antigen binding fragment, and

b) recovering the antibody or antigen binding fragment comprising the non-human variable domain comprising the modified FR from the host cell, wherein the modified antibody or antigen binding fragment has improved folding efficiency and yield in the cell or cell culture as compared to the folding efficiency and yield of an unmodified antibody or antigen binding fragment.

Claim 97 (previously presented): The method according to claim 96, wherein: (a) the nucleic acid is contained in an expression vector, (b) the nucleic acid is operably linked to a promoter, (c) the method of (a) or (b), wherein the nucleic acid further comprises a heat stable enterotoxin sequence that can direct secretion to the periplasm, or (d) the method of any of (a) to (c), wherein the nucleic acid further comprises a terminator sequence.

Claim 98 (previously presented): The method according to claim 96, wherein the host cell is a prokaryotic host cell.

Claim 99 (previously presented): The method according to claim 96, wherein the host cell is a eukaryotic host cell.

Claim 100 (currently amended): A method for improving the yield of an antibody or antigen binding fragment in a host cell or cell culture, comprising:

(A) expressing a nucleic acid molecule encoding a modified variable domain of a non-human antibody or antigen binding fragment in the host cell or cell culture, wherein the modified

variable domain has: (i) a substitution of at least one but not all amino acids proximal to a cysteine (cys) reside that participates in an intrachain variable domain disulfide bond with a different amino acid, or (ii) deleting at least one but not all amino acids proximal to a cys reside that participates in an intrachain variable domain disulfide bond, wherein the substituted or deleted amino acid is determined by:

(a) aligning a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) sequence of the variable domain of the non-human antibody or antigen binding fragment to corresponding HVR1 and/or HVR2 sequences of human subgroup variable domain consensus sequences, and

(b) selecting the amino acid found at the corresponding position of the human subgroup variable domain consensus sequence that has a HVR1 and/or HVR2 amino acid sequence with the most sequence identity with the HVR1 and/or HVR2 amino acid sequence of the non-human variable domain as the different amino acid, and

(B) recovering the antibody or antigen binding fragment comprising the modified variable domain from the host cell, wherein the antibody or antigen binding fragment has improved folding efficiency and yield in the host cell or cell culture as compared to the folding efficiency and yield of a [[the]] corresponding unmodified antibody or antigen binding fragment.

Claim 101 (previously presented): The method according to claim 100, wherein: (a) the host cell comprises an expression vector that comprises the nucleic acid molecule encoding the modified variable domain; (b) the nucleic acid molecule encoding the modified variable domain is operably linked to a promoter, (c) the method of (a) or (b), wherein the nucleic acid further comprises a heat stable enterotoxin sequence that can direct secretion to a periplasm of the host cell, or (d) the method of any of (a) to (c), wherein the nucleic acid further comprises a terminator sequence.

Claim 102 (previously presented): The method according to claim 100, wherein the host cell is a prokaryotic host cell.

Claim 103 (previously presented): The method according to claim 100, wherein the host cell is a eukaryotic host cell.

Claim 104 (currently amended): A method for improving the yield of a non-human antibody, or antigen binding fragments thereof, in a host cell or cell culture comprising:

(a) comparing a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) amino acid sequence of a heavy chain variable domain of the non-human antibody or antigen binding fragment to a corresponding HVR1 and/or HVR2 amino acid sequence of each human subgroup heavy chain variable domain consensus sequence and selecting the human subgroup heavy chain variable domain consensus sequence that has the most sequence identity with the HVR1 and/or HVR2 sequence of the heavy chain variable domain of the non-human antibody or antigen binding fragment;

(b) identifying at least one amino acid position in at least one framework (FR) in the heavy chain variable domain of the non-human antibody or antigen binding fragment selected from the group consisting of a FR1, a FR2, a FR3, a FR4 and a mixture thereof, wherein the amino acid position has a different amino acid than the amino acid at a corresponding position of the selected human subgroup heavy chain variable domain consensus sequence; and

(c) modifying or deleting at least one but not all of the amino acid positions identified in step (b), wherein the modification or deletion is with the amino acid in the corresponding position of the selected human heavy chain subgroup variable domain consensus sequence, to form a variable domain with a modified FR; and

(d) expressing the antibody or antigen binding fragment comprising the heavy chain variable domain with the modified FR in the host cell or cell culture, and

(e) recovering the antibody or antigen binding fragment from the host cell or cell culture,

wherein the antibody or antigen binding fragment with the modified FR has improved yield in the host cell or cell culture compared to the folding efficiency and yield of a corresponding unmodified non-human antibody or antigen binding fragment.

Claim 105 (previously presented): The method according to claim 104, wherein the non-human antibody is selected from the group consisting of a humanized antibody, a chimeric antibody, a monoclonal antibody, a multispecific antibody, a diabody, or an antibody generated by phage display.

Claim 106 (previously presented): The method according to claim 105, wherein the non-human antigen binding fragment is a Fab fragment, $F(ab')_2$ fragment, scFV fragment, or $sc(Fv)_2$ fragment, single arm antibody, or single chain antibody.

Claim 107 (previously presented): The method according to claim 104, wherein the non-human antibody is an anti-VEGF antibody.

Claim 108 (previously presented): The method according to claim 107, wherein the non-human antibody is a humanized antibody.

Claim 109 (previously presented): The method of claim 104, wherein step (c) comprises modifying a nucleic acid encoding the non-human variable domain to form a nucleic acid encoding a variable domain with a modified FR, wherein the modified FR has at least one but not all of the amino acid positions: (i) substituted with the amino acid in the corresponding position of the selected human subgroup variable domain consensus sequence; or (ii) deleted.

Claim 110 (previously presented): The method of claim 109, wherein the variable domain-encoding nucleic acid further comprises a nucleic acid encoding a constant region domain, and the constant region domain-encoding nucleic acid is connected to the nucleic acid encoding the variable domain with the modified FR to form a nucleic acid encoding a variant full-length heavy or light chain.

Claim 111 (previously presented): The method of claim 109, wherein the modified nucleic acid is comprised within an expression vector.

Claim 112 (previously presented): The method of claim 111, further comprising culturing a host cell comprising the expression vector or the modified nucleic acid under conditions wherein the antibody chains are expressed; and recovering a full-length heavy or light chain or both from the cell or cell culture.

Claim 113 (original): The method according to claim 112, wherein the host cell is a prokaryotic host cell.

Claim 114 (original): The method according to claim 112, wherein the host cell is a mammalian cell.

Claim 115 (canceled)

Claim 116 (previously presented): The method according to claim 104, wherein the variable domain is a heavy chain variable domain and the HVR1 amino acid sequence is GYTFTNYGIN (SEQ ID NO: 14) or GYDFTHYGMN (SEQ ID NO:18).

Claim 117 (previously presented): The method according to claim 104, wherein the framework region is selected from the group consisting of FR1, FR2, FR3, and a mixture thereof.

Claim 118 (previously presented): The method according to claim 117, wherein the human subgroup FR consensus sequence is a heavy chain FR1 sequence with a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3.

Claim 119 (previously presented): The method according to claim 104, wherein the yield of the antibody or antigen binding fragment with the modified FR is improved at least 2 fold compared to the corresponding unmodified antibody or antigen binding fragment.

Claim 120 (previously presented): The method according to claim 119, wherein the yield of the antibody or antigen binding fragment with the modified FR is improved at least 2 fold to 16 fold compared to the corresponding unmodified antibody or antigen binding fragment.

Claim 121 (previously presented): The method of claim 104, wherein at least two but not all of the identified amino acid positions in at least one FR of the non-human antibody or antigen binding fragment are: (i) substituted with amino acids in the corresponding position of the selected human subgroup consensus sequence, or (ii) deleted.

Claim 122 (previously presented): The method of claim 121, wherein the non-human antibody or antigen binding fragment is a VEGF antibody or antigen binding fragment that comprises a heavy chain variable domain FR1 comprising the amino acid sequence of SEQ ID NO:3, and the FR is a heavy chain FR1 and one of the identified amino acid positions is position 6 or position 23 or both, and the other position is selected from the group consisting of position 1, 11, 13, 18, 19, and a mixture thereof.

Claim 123 (original): The method of claim 122 wherein amino acid positions 6 and 23 are substituted.

Claim 124 (original): The method of claim 122, wherein all of the amino acid positions at position, 1, 6, 11, 13, 18, 19, and 23 of the heavy chain FR1 are substituted.

Claim 125 (previously presented): The method of claim 104, wherein at least three but not all of the identified amino acid positions in a FR are: (i) substituted with the amino acid in the corresponding position in the selected human subgroup consensus sequence, or (ii) deleted.

Claim 126 (previously presented): The method of claim 125, wherein the FR is a FR1, a FR2, or a FR3.

Claim 127 (previously presented): The method of claim 104, wherein at least four but not all of the identified amino acid positions in all FR are: (i) substituted with the amino acid in the corresponding position in the selected subgroup consensus sequence, or (ii) deleted.

Claim 128 (canceled)

Claim 129 (previously presented): The method of claim 104 further comprising:

(a) comparing a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) amino acid sequence of a light chain variable domain of a non-human antibody or antigen binding fragment to a corresponding HVR1 and/or HVR2 amino acid sequence of a human subgroup light chain variable domain consensus sequence and selecting the human subgroup light chain variable domain consensus sequence that has the most sequence identity with the HVR1 and/or HVR2 sequence of the non-human light chain variable domain;

(b) identifying at least one amino acid position in at least one FR in the non-human light chain variable domain selected from the group consisting of a FR1, a FR2, a FR3, a FR4 and a mixture thereof, wherein the amino acid position has a different amino acid than the amino acid at a corresponding position of the selected human subgroup light chain variable domain consensus sequence; and

(c) (i) modifying the at least one but not all of the non-human amino acid positions identified in step (b) with the amino acid in the corresponding position of the selected human subgroup light chain variable domain consensus sequence to form a modified light chain variable domain with a modified FR, or (ii) deleting the at least one but not all of the non-human amino acid positions identified in step (b).

Claim 130 (currently amended): A method for improving the yield of a recombinant non-human antibody or antigen-binding fragment thereof <u>in a host cell or cell culture</u>, comprising:

(a) identifying at least one amino acid position in a heavy chain variable domain of the non-human antibody or antigen binding fragment that is proximal to a cysteine (cys) residue that participates in an intrachain disulfide bond in the heavy chain variable domain;

(b) aligning a hypervariable region 1 (HVR1) and/or hypervariable region 2 (HVR2) of the non-human heavy chain variable domain of step a) to corresponding HVR1 and/or HVR2 sequences of human subgroup heavy chain variable domain consensus sequences;

(c) selecting the human subgroup heavy chain variable domain consensus sequence having the most identity with the HVR1 and/or HVR2 amino acid sequence of the non-human heavy chain variable domain;

(d) modifying at least one but not all of the amino acid positions in the non-human heavy chain variable domain an amino acid found at the corresponding position in the selected human subgroup heavy chain variable domain consensus sequence to form a modified non-human heavy chain variable domain; and

(e) expressing the antibody or antibody fragment thereof comprising the modified non-human heavy chain variable domain, wherein the modified non-human antibody or antibody fragment thereof has improved folding efficiency and yield in the **[[a]]** host cell or cell culture as compared to the folding efficiency and yield of a corresponding unmodified antibody or antibody fragment.

Claim 131 (previously presented): The method of claim 1, wherein the host cell is a prokaryotic cell or a eukaryotic cell.

Claim 132 (previously presented): The method of claim 131, wherein the host cell is a filamentous fungi or yeast cell, an insect cell, a mammalian cell or a bacterial cell.

Claim 133 (previously presented): The method of claim 132, wherein the host cell is an *Archaebacteria* or a *Eubacteria*, or a Gram-negative or a Gram-positive organism.